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09/550,173	04/14/2000	Norihisa Ooe	2185-0424-SP	8838
<div>7590 12/28/2006 Birch Stewart Kolasch &amp; Birch LLP P O Box 747 Falls Church, VA 22040-0747</div>			<div>EXAMINER SCHLAPKOHL, WALTER</div>	
			<div>ART UNIT 1636</div>	<div>PAPER NUMBER.</div>
SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE		
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

<b>Office Action Summary</b>	Application No.	Applicant(s)	
	09/550,173	OOE ET AL.	
	Examiner	Art Unit	
	Walter Schlapkohl	1636	<i>WLF</i>

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 10 October 2006.
- 2a) ☐ This action is FINAL.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-9, 11-17 and 19-29 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-9, 11-17 and 19-29 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)          | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

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#### DETAILED ACTION

Receipt is acknowledged of the papers filed 10/10/2006 in which claims 11-12, 14-15 and 17 were amended, and claims 20-29 were added. Claims 10 and 18 are cancelled. Claims 1-9, 11-17 and 19-29 are pending and under examination in the instant Office action.

Any rejection of record not set forth herein is hereby WITHDRAWN.

#### *Specification*

The objection to the specification under 35 U.S.C. 132(a) is WITHDRAWN in view of Applicant's amendment.

#### *Sequence Compliance*

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because sequences are set forth in the in the form of GENBANK accession numbers and are not accompanied by SEQ ID NOs. This is a new objection which has been raised by the amendment of the claims now drawn to nucleic acid sequences

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not present in the Sequence Listing (see, e.g., recitation of "a nucleotide sequence from 33 base upstream to 15 base downstream of the transcription initiation point in the 5' upstream region of mouse metallothionein I gene" in claim 22 and recitation of "a nucleotide sequence from 50 base upstream to 10 base downstream of the transcription initiation point in the 5' upstream region of chicken ovalbumin gene" in claim 24).

Examiner understands support for these new claims to come from the 1<sup>st</sup> full paragraph on page 17 of the marked-up copy of the substitute specification wherein Applicant discloses examples of "minimum promoter" nucleotide sequences including "nucleotide sequences (Genbank Accession No. J00605) from -33 base (Transcription initiation point is +1. Hereinafter, the same.) to +15 base in the 5' upstream region of metallothionein I gene of mouse, nucleotide sequences (Genbank Accession No. J00895) from -40 base to +10 base in the 5' upstream region of chicken ovalbumin gene and the like." It is noted for the record that the sequences recited by Applicant have been altered after the filing date of the instant application (see comment section of Genbank Accession Entries J00895 and J00605).

Applicant is required to comply with all of the requirements of 37 CFR 1.821 - 1.825. Any response to this Office action that fails to meet all of these requirements will be considered non-

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responsive. The nature of the noncompliance with the requirements of 37 C.F. R. 1.821 through 1.825 did not preclude the examination of the application on the merits, the results of which are communicated below.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11-12, 14, 22, 24 & 27-28, and therefore dependent claims 15-16 & 29, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. **Any new basis for rejections made herein was necessitated by Applicant's amendment to the claims.**

Claim 11 recites "[a] method for evaluating a chemical substance to have agonist activity over the transcription promoting ability of a ligand-responsive transcription control factor, said method comprising:

(i) culturing an animal cell according to any one of claims 1 to 9 in the presence of the chemical substance;

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(ii) measuring the expression amount of reporter gene (a) in said cell and

(iii) assessing said chemical substance to have agonist activity over the transcription promoting ability of the ligand-responsive transcription control factor when the value of expression amount measured in the step (ii) of said reporter gene (a) introduced into said cell is larger than a measured value of expression amount of said reporter gene (a) in the absence of said chemical substance" in lines 1-11 (emphasis added). Claim 11 is vague and indefinite for two reasons. First, as recited in the previous Office action, it is unclear which values of expression amounts are actually being compared. Can any value of expression amount of said reporter gene (a) in the absence of said chemical substance be used in a comparison against the value obtained in step (ii)? Second, as a result of Applicant's amendment, the claim is rendered indefinite in that it is unclear what Applicant intends by "the value of expression amount measured in the step (ii) of said reporter gene (a)" in lines 8-9. Does Applicant intend "the value of expression amount of said reporter gene (a) introduced into said cell as measured in step (ii)" or does Applicant intend a reporter gene (a) comprising a "step (ii)"?

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Claim 12 is also vague and indefinite for the reasons cited above for claim 11.

Claim 14 recites "[a] method for obtaining an animal cell for measuring the ability to control the activity of a ligand-responsive transcription control factor, said method comprising:

(i) introducing into an animal cell, a DNA comprising in a molecule the following genes (a) and (b):

(a) a reporter gene connected downstream from a transcription control region, wherein said transcription control region substantially consists of a recognition sequence of said ligand-responsive transcription control factor and a minimum promoter which can function in said cell, and

(b) a selective marker gene which can function in said cell,

said animal cell being an animal cell into which a DNA comprising a gene coding the ligand-responsive control factor is introduced before, after or during the same time of the step (i) or an animal cell that naturally has an ability to express the gene coding the ligand-responsive transcription control factor. Provided that a reporter gene (c) connected downstream from a promoter which transcription activity is unchanged by having said ligand-responsive transcription control factor, said reporter gene (c) coding a protein which can be differentiated

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from the protein coded by said gene (a), is not present in the cell; and

(ii) recovering from the transformed cell obtained from step (i), a transformed cell having said introduced DNA stably maintained therein" in lines 1-22 (emphasis added). Claim 14 is vague and indefinite in that there is insufficient antecedent basis for the limitation "said introduced DNA" in line 22 of the claim. Does Applicant intend the introduced DNA comprising genes (a) and (b), the introduced ligand-responsive control factor or both?

Similarly, claims 27 and 28 are vague and indefinite because there is insufficient antecedent basis for the limitation "said introduced DNA" in line 21 of each claim, as explained for claim 14 above.

Claim 22 recites "[t]he cell according to any one of claims 1, 2, 9, 17 and 20, wherein said minimum promoter has a nucleotide sequence from 33 base upstream to 15 base downstream of the transcription initiation point in the 5' upstream region of mouse metallothionein I gene" in lines 1-3 (emphasis added). Claim 22 is vague and indefinite in that it is unclear whether Applicant intends a minimum promoter that has a nucleotide sequence from 33 bases upstream to 15 bases downstream of the transcription initiation point in the 5' upstream region of any

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mouse metallothionine gene or only the mouse metallothionine I gene of Genbank Accession No. J00605 (see page 17, 1<sup>st</sup> full paragraph of the marked-up copy of the substitute specification and the attached Genbank Accession entry J00605)? If the latter, did Applicant intend the J00605 sequence according to the original submission, according to the updated sequence which replaced gi:53247 on or before 2/2/2004, or both?

Similarly, claim 24 recites "[t]he cell according to any one of claims 1, 2, 9, 17 and 21, wherein said minimum promoter has a nucleotide sequence from 40 base upstream to 10 base downstream of the transcription initiation point in the 5' upstream region of chicken ovalbumin gene" in lines 1-3 (emphasis added). Does Applicant intend a minimum promoter that has a nucleotide sequence from 40 bases upstream to 15 bases downstream of the transcription initiation point in the 5' upstream region of any chicken ovalbumin gene or the chicken ovalbumin gene of Genbank Accession No. J00895 (see page 17, 1<sup>st</sup> full paragraph of the marked-up copy of the substitute specification as well as the attached Genbank Accession entry J00895)? If the latter, did Applicant intend the J00895 sequence according to the original submission, according to the updated sequence which replaced gi:341287 on 2/8/2002, or both?

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*Response to Arguments*

Applicant traverses the rejections made under 35 U.S.C. 112, Second Paragraph, and further argues that the disputed claim language has been clarified. As an example, Applicant notes that the value of expression amount in claim 11 has been amended to indicate that "the value of expression amount of step (iii) is what is measured in the previous step" (see paragraph bridging pages 21-22 of the remarks filed 10/10/2006).

Applicant's arguments have been carefully considered and are respectfully found unpersuasive. Applicant's amendment has gone part way to addressing the rejection of claims 11-12 under 35 U.S.C. 112, Second Paragraph, but there were in fact two expression amounts which required clarification. The amount of expression measured in step (ii) of the claims (now clear and definite) and the amount of expression of the reporter gene (a) in the absence of said chemical substance which appears to be any measure as explained above.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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Claim 19 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection. This rejection is maintained for reasons of record.**

The specification as originally filed does not provide support for the invention as now claimed: "[t]he cell according to any one of claims 1, 2, 9 and 17, wherein said minimum promoter is a minimum promoter of metallothionein I gene or ovalbumin gene." The specification does not provide sufficient blazemarks nor direction for the instant minimum promoters encompassed by the above-mentioned limitation, as currently recited. The instant specification only provides sufficient blazemarks and direction for minimal promoters of the mouse metallothionein I gene and chicken ovalbumin gene. The instant claims now recite a limitation, which was not clearly disclosed in the specification as filed, and now changes the scope of the instant disclosure as filed. Such a limitation recited in the present claims, which did not appear in the specification as

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filed, introduces new concepts and violates the description requirement of the first paragraph of 35 U.S.C. 112.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 11-17 and 19-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **The additional grounds of rejection set forth herein were not necessitated by Applicant's amendment to the claims.**

The claims are drawn to animal cells expressing a gene coding a ligand-responsive transcription control factor and stably transformed with a DNA comprising:

gene (a) which is a reporter gene connected downstream from a transcription control region which consists substantially of a recognition sequence of said ligand responsive transcription

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control factor and a minimum promoter which can function in said cell and

gene (b) which is a selective marker gene which can function in said cell;

provided that the following gene (c) is NOT present in said cell: a reporter gene connected downstream from a promoter which transcription activity is unchanged by having said ligand-responsive transcription control factor contacted with a ligand of said ligand-responsive transcription control factor, said reporter gene (c) coding a protein which can be differentiated from the protein coded by said gene (a). The claims encompass 1) any transcription control region which contains any ligand-responsive transcription factor recognition sequence and any minimum promoter as the "main functional element relating to transcription control" (see page 18, 1<sup>st</sup> full paragraph of the marked-up copy of the substitute specification). The ligand-responsive transcription control factor recognition sequence is "a specific nucleotide sequence present in the transcription control region of a target gene which the expression amount is controlled by a ligand-responsive transcription control factor, and when a complex ligand of a ligand and a ligand-responsive transcription control factor recognizes this sequence and binds thereto, the transcription of a target gene present in the

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downstream therefrom is promoted" (see paragraph bridging pages 15-16 of the marked-up copy of the substitute specification), which Examiner understands to encompass any nucleotide sequence which is part of any transcription control region which promotes expression of a gene when bound to a ligand-responsive transcription control factor, i.e. any nucleotide sequence which is a part of any such sequence. The "minimum promoter" is defined as "a DNA having a region which determines the transcription initiation site by RNA polymerase II and relates to maintaining a minimum transcription level" (see page 17, 1<sup>st</sup> full paragraph of the marked-up copy of the substitute specification). Thus, the claims encompass any "gene (a)" comprising any reporter gene operably linked to any DNA having a region which determines the transcription initiation site by RNA polymerase II (minimum promoter) in combination with any nucleotide sequence which is a part of any ligand-responsive transcription control factor recognition sequence.

Furthermore the claims encompass cells which do NOT comprise a reporter gene ("gene (c)") which is connected downstream from a promoter which transcription activity is unchanged by having said ligand-responsive transcription control factor contacted with a ligand of said ligand-responsive transcription control factor, said reporter gene (c) coding a

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protein which can be differentiated from the protein coded by said gene (a). Although Applicant has defined a "promoter which transcription activity is unchanged by having said ligand-responsive transcription control factor contacted with a ligand of said ligand-responsive transcription control factor" on pages 26-27 of the marked-up copy of the substitute specification as "a promoter which is not controlled by the recognition sequence of the ligand-responsive transcription control factor as described above and has constitutive transcription ability...", this definition still means that gene (c), when given its broadest reasonable interpretation, encompasses any gene, endogenous or exogenous, which is driven by a constitutive promoter and which expresses a protein that can be differentiated from the protein encoded by gene (a). Based on the fact that any animal cell would comprise endogenous genes which are constitutively expressed and which encode proteins that could be differentiated from any exogenous reporter gene, it is not clear that Applicant, at the time the application was filed, was in possession of the claimed animal cell. The claims do not provide any structural information with regard to animal cells which do not comprise the recited gene (c). Thus, the rejected claims also comprise a set of animal cells comprising the recited genes (a) and (b) in a DNA molecule that are defined

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by the absence of a reporter gene operably linked to a constitutive promoter and which encodes a protein that can be differentiated from the protein encoded by gene (a).

In addition to the issues raised above, the claims are drawn to genes coding a ligand responsive transcription factor (LRTF) and stably transformed with a reporter gene and a selective marker gene. The claims do not provide any structural information with regard to the genes (promoters, enhancers, exon and intron sequences and boundaries, 3' untranslated regions) capable of being expressed in and/or stably transformed in a molecule or within the claimed animal cells. Thus, the rejected claims also comprise a set of nucleic acid sequences that are defined by the coding region of a gene.

The claims are also drawn to methods for making an animal cell with the above-cited features as well as methods for evaluating a chemical substance's activity over the transcription promoting ability of a ligand-responsive transcription control factor comprising the use of such a cell.

As a whole, the skilled artisan would not have been able to describe the broadly claimed genus of nucleic sequences that can be stably transformed into an animal cell such that the animal cell can be used to detect differences in a chemical substance's activity over the transcription promoting ability of any ligand-

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responsive transcription control factor. Thus, there is no structural/functional basis provided by the prior art or instant specification for one of skill in the art to envision those nucleic acid sequences in combination with those animal cells that satisfy the functional limitations of the claims.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. The specification describes plasmids comprising in a molecule both an LRTF recognition sequence (e.g. from an aryl hydrocarbon receptor) and a minimum promoter (e.g., from a mouse metallothionein I gene) operatively linked to a reporter "gene" (e.g., the firefly luciferase coding region) transfected into NIH 3T3, MCF7, or HeLa cells.

However, no description is provided of a single animal cell comprising an entire gene sequence for an LRTF and which has been stably transformed with the entire gene sequence for a reporter gene and/or a marker gene. The specification does not describe the genes themselves, including the 5' and 3' elements

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as well as the introns and exons and their corresponding sequences.

No description is provided of sequences required for a LRTF recognition sequence.

Most conspicuously, there is no description of an animal cell which does NOT comprise a "reporter gene" operably linked to a constitutive promoter and which encodes a protein that can be differentiated from the protein encoded by the recited gene (a).

Even if one accepts that the examples described in the specification meet the claim limitations of the rejected claims with regard to structure and function, the examples are only representative of a few combinations of minimum promoters (mouse metallothionein I, chicken ovalbumin) and ligand-responsive transcription control factor recognition sequences (estrogen receptor, aryl hydrocarbon, etc.). The results are not necessarily predictive of any other sequences capable of being stably transformed into a cell which does NOT comprise a gene (c), gene (c) comprising a reporter gene connected downstream from a constitutive promoter and encoding a protein which can be differentiated from gene (a), and further wherein the cell can be used to evaluate a chemical substance's activity over the transcription promoting ability of a ligand-responsive

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transcription control factor, the animals sole claimed utility. Thus, it is impossible to extrapolate from the example(s) described herein those nucleic acid molecules/animal cells that would necessarily meet the structural/functional characteristics of the rejected claims.

The prior art does not appear to offset the deficiencies of the instant specification in that it does not describe a set of nucleic acids or genes or animals that do not comprise the recited gene (c) but which are capable of evaluating a chemical substances antagonist activity over a ligand-responsive transcription control factor. Mader et al (US Patent No. 5,512,483; of record) describe a cell comprising a mammalian expression vector composed of several high affinity glucocorticoid response elements placed upstream of a minimal promoter TATA region and which further comprises a reporter gene (CAT) and a selective marker gene (see entire document, especially paragraph bridging columns 2 and 3 and Figure 1). However, Mader et al do not teach such a cell wherein the cell does not comprise a reporter gene connected downstream from a promoter which transcription activity is not changed by having said LRTF contacted with a ligand of said LRTF.

Given the very large genus of nucleic acid molecules encompassed by the rejected claims, and given the limited

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description provided by the prior art and specification with regard to the sequences and animal cells capable of fulfilling the claim limitations of claims 1-9, 11-17 and 19-29, the skilled artisan would not have been able to describe the broadly claimed genus of nucleic sequences that can be stably transformed into an animal cell such that the animal cell can be used to detect differences in a chemical substance's activity over the transcription promoting ability of any ligand-responsive transcription control factor. Thus, there is no structural/functional basis provided by the prior art or instant specification for one of skill in the art to envision those nucleic acid sequences in combination with those animal cells that satisfy the functional limitations of the claims. Therefore, the skilled artisan would have reasonably concluded Applicant was not in possession of the claimed invention for claims 1-9, 11-17 and 19-29.

Claims 1-9, 11-17 and 19-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is

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most nearly connected, to make and/or use the invention. **This is a new rejection not necessitated by Applicant's amendment.**

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art, the amount of experimentation necessary and the relative skill levels of those in the art. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

*Nature of the Invention:* The claims are drawn to animal cells expressing a gene coding a ligand-responsive transcription control factor and stably transformed with a DNA comprising:

gene (a) which is a reporter gene connected downstream from a transcription control region which consisting substantially of a recognition sequence of said ligand responsive transcription control factor and a minimum promoter which can function in said cell and

gene (b) which is a selective marker gene which can function in said cell;

provided that the following gene (c) is NOT present in said cell: a reporter gene connected downstream from a promoter which transcription activity is unchanged by having said ligand-

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responsive transcription control factor contacted with a ligand of said ligand-responsive transcription control factor, said reporter gene (c) coding a protein which can be differentiated from the protein coded by said gene (a).

The claims are also drawn to methods for making an animal cell with the above-cited features as well as methods for evaluating a chemical substance's activity over the transcription promoting ability of a ligand-responsive transcription control factor, the methods comprising the use of such a cell.

*Breadth of the claims:* The claims are drawn to an extremely broad genus of nucleic acids that encompass 1) any transcription control region which contains any ligand-responsive transcription factor recognition sequence and any minimum promoter as the "main functional element relating to transcription control" (see page 18, 1<sup>st</sup> full paragraph of the marked-up copy of the substitute specification). As explained above, Examiner understands such sequences to encompass any nucleotide sequence which is a part of any transcription control region which promotes expression of a gene when bound to a ligand-responsive transcription control factor. The "minimum promoter" is defined as "a DNA having a region which determines the transcription initiation site by RNA polymerase II and

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relates to maintaining a minimum transcription level" (see page 17, 1<sup>st</sup> full paragraph of the marked-up copy of the substitute specification). Thus the claims encompass any "gene (a)" comprising any reporter gene operably linked to any DNA having a region which determines the transcription initiation site by RNA polymerase II (minimum promoter) in combination with any nucleotide sequence which is a part of any ligand-responsive transcription control factor recognition sequence.

Furthermore the claims encompass cells which do NOT comprise a reporter gene ("gene (c)") which is connected downstream from a promoter which transcription activity is unchanged by having said ligand-responsive transcription control factor contacted with a ligand of said ligand-responsive transcription control factor, said reporter gene (c) coding a protein which can be differentiated from the protein coded by said gene (a). Although Applicant has defined a "promoter which transcription activity is unchanged by having said ligand-responsive transcription control factor contacted with a ligand of said ligand-responsive transcription control factor" on pages 26-27 of the marked-up copy of the substitute specification as "a promoter which is not controlled by the recognition sequence of the ligand-responsive transcription control factor as described above and has constitutive transcription ability...",

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this definition still means that gene (c), when given its broadest reasonable interpretation, encompasses any gene (endogenous or exogenous) which is driven by a constitutive promoter and which expresses a protein that can be differentiated from the protein encoded by gene (a). Insofar as any animal cell would certainly comprise endogenous genes which are constitutively expressed and which encode proteins that could be differentiated from any exogenous reporter gene, the claims also include a very narrow genus of such cells.

*Guidance of the specification/The existence of working examples:* The specification describes plasmids comprising in a molecule both an LRTF recognition sequence (e.g. from an aryl hydrocarbon receptor) and a minimum promoter (e.g., from a mouse metallothionein I gene) operatively linked to a reporter "gene" (e.g., the firefly luciferase coding region) transfected into NIH 3T3, MCF7 or HeLa cells.

However, the specification fails to teach a single animal cell comprising an entire gene sequence for an LRTF and which has been stably transformed with the entire gene sequence for a reporter gene and/or a marker gene.

Outside of the examples provided (e.g, the estrogen receptor LRTF recognition sequence used in combination with the mouse metallothionein I minimum promoter), the specification

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fails to provide any guidance as to which minimum promoter nucleic acid sequences used in combination with which LRTF recognition sequences could be used such that differences in a chemical substance's ability to activate LRTF-induced promoter activity could be evaluated.

Most conspicuously, the specification fails to provide any guidance whatsoever of an animal cell which does NOT comprise a "reporter gene" operably linked to a constitutive promoter and which encodes a protein that can be differentiated from the protein encoded by the recited gene (a).

*State of the prior art:* The literature reports examples of ligand-responsive transcription factors coupled to minimum promoters for inducing reporter gene expression. The literature also reports such nucleic acids wherein the nucleic acid molecule further comprises a selective marker gene. For example, Mader et al (US Patent No. 5,512,483; of record) describe a cell comprising a mammalian expression vector composed of several high affinity glucocorticoid response elements placed upstream of a minimal promoter TATA region and which further comprises a reporter gene (CAT) and a selective marker gene (see entire document, especially paragraph bridging columns 2 and 3 and Figure 1). However, Mader et al do not teach such a cell wherein the cell does not comprise a reporter

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gene connected downstream from a promoter which transcription activity is not changed by having said LRTF contacted with a ligand of said LRTF.

*Predictability of the art/Amount of experimentation necessary:*

Because such an animal cell is not taught in the prior art, one of ordinary skill in the art would be required to perform an undue and burdensome amount of experimentation in order to first generate such an animal cell such that the cell could be stably transformed with the recited genes (a) and (b) comprising the claimed LRTF recognition sequences and the claimed minimum promoter sequences. Such a task would be accompanied by a definitive lack of predictive success.

However, should one of ordinary skill in the art succeed in such an undertaking, he or she would then have to determine which of the broad genus of encompassed LRTF recognition sequences in combination with which of the minimum promoter sequences could be used to generate and use such a cell in methods for measuring and evaluating the ability to control the activity of a ligand-responsive transcription control factor.

Given the complex nature of invention and the underdeveloped state of the art at the time of filing, there would be a large and prohibitive amount of experimentation required to make and use the claimed invention.

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***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 5, 13-14 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Mader and White (US Patent No. 5,512,483; of record). **This rejection is maintained for reasons of record and extended to new claims 25-28.**

NOTE: For this rejection only, Examiner has interpreted the claims to encompass animal cells stably transformed with a DNA comprising in a molecule, a reporter gene (a) connected downstream from a transcription control region, in which said transcription control region contains a ligand-responsive transcription control factor recognition sequence and a minimum promoter as the main functional element relating to transcription control and a selectable marker (b), but does not contain a reporter gene (c) which is not responsive to said transcription response element, said reporter gene encoding an

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an exogenous reporter protein such as CAT or luciferase or the equivalent.

The Mader et al reference anticipates the rejection of newly added claims 25-28 because Mader et al teach that the promoter used was 50 fold inducible (i.e., more than 5 or 10 fold inducible) in the presence of ligand for the ligand-responsive transcription control factor (see Mader et al at column 3, lines 12-15).

#### *Response to Arguments*

Applicant argues that the Mader reference does not disclose all instantly claimed features. Specifically, Applicant argues that the expression vector disclosed by Mader does not have any "selective marker gene which can function in [an animal] cell" as instantly claimed. Applicant argues that the ampicillin resistance marker contained in the disclosed expression vector is a selection marker in bacterial cells, not animal cells.

Applicant's arguments have been carefully considered but have been respectfully found unpersuasive. On page 19, 2<sup>nd</sup> full paragraph of the marked-up copy of the substitute specification, Applicant defines "selective marker gene" as "a gene coding a phenotype which can be a mark in differentiating a cell which has been transformed by DNA containing the gene from a non-

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transformed cell." This definition does not rule out an ampicillin resistance gene just because an animal cell is resistant to ampicillin with or without its expression. Certainly the gene coded by the ampicillin resistance gene can be expressed in an animal cell and the expressed protein can be detected as a "mark in differentiating a cell which has been transformed by DNA containing the gene from a non-transformed cell." One of ordinary skill in the art could, e.g., decide to use PCR or Western blotting to detect the selective marker gene as a "mark in differentiating a cell which has been transformed by DNA containing the gene from a non-transformed cell."

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-9, 11 and 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bradfield et al (US Patent No. 5,650,283; of record) in view of Waldman and Waldman (*Analytical Biochemistry* 258:216-222, 1998; of record).

**This rejection is maintained for reasons of record.**

NOTE: For this rejection only, Examiner has interpreted the claims to encompass animal cells stably transformed with a DNA comprising in a molecule, a reporter gene (a) connected downstream from a transcription control region, in which said transcription control region contains a ligand-responsive transcription control factor recognition sequence and a minimum promoter as the main functional element relating to

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transcription control and a selectable marker (b), but does not contain a reporter gene (c) which is not responsive to said transcription response element, said reporter gene encoding an an exogenous reporter protein such as CAT or luciferase or the equivalent.

Claims 1-9, 11-12 and 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bradfield et al (US Patent No. 5,650,283, of record; henceforth Bradfield) in view of Waldman and Waldman (*Analytical Biochemistry* 258:216-222, 1998; of record) and further in view of Kushner et al (US Patent 6,117,638; of record).

**This rejection is maintained for reasons of record.**

NOTE: For this rejection only, Examiner has interpreted the claims to encompass animal cells stably transformed with a DNA comprising in a molecule, a reporter gene (a) connected downstream from a transcription control region, in which said transcription control region contains a ligand-responsive transcription control factor recognition sequence and a minimum promoter as the main functional element relating to transcription control and a selectable marker (b), but does not contain a reporter gene (c) which is not responsive to said transcription response element, said reporter gene encoding an

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an exogenous reporter protein such as CAT or luciferase or the equivalent.

Claims 1, 3-9, 11, 14-17 and 19 and 21, 25-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bradfield et al (US Patent No. 5,650,283; of record) in view of Waldman and Waldman (*Analytical Biochemistry* 258:216-222, 1998; of record) and further in view of O'Malley et al (US Patent 5,834,213; of record).

**This rejection is maintained for reasons of record and extended to new claims 21 and 25-29.**

NOTE: For this rejection only, Examiner has interpreted the claims to encompass animal cells stably transformed with a DNA comprising in a molecule, a reporter gene (a) connected downstream from a transcription control region, in which said transcription control region contains a ligand-responsive transcription control factor recognition sequence and a minimum promoter as the main functional element relating to transcription control and a selectable marker (b), but does not contain a reporter gene (c) which is not responsive to said transcription response element, said reporter gene encoding an an exogenous reporter protein such as CAT or luciferase or the equivalent.

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The combination of references above anticipates the newly added claims because 1) Mader et al teach that the promoter used was 50 fold, (i.e. more than 5 or 10 fold) inducible in the presence of ligand for the ligand-responsive transcription control factor (see Mader et al at column 3, lines 12-15). Furthermore, the ovalbumin taught by O'Malley et al is that of chicken (see, e.g., O'Mally et al at column 3, lines 11-14 and Figure 4).

#### *Response to Arguments*

Applicant argues that the reporter gene (a) of the instant claims is connected downstream from a transcription control region which substantially consists of a recognition sequence of the ligand-responsive transcription control factor and a minimum promoter, and that, as such, the constitutive background transcription activity is lowered. Applicant further argues that the lower background activity allows for higher sensitivity in the detection of ligand-responsive transcription activity. Applicant further argues that the prior-cited reference, whether alone or in combination, fail to suggest or disclose the presently claimed subject matter, and that the references fail to recognize the fact that the present animal cell exhibits higher sensitivity in the detection of ligand-responsive

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transcription activity. Applicant further argues that the cited art fails to suggest or disclose a DNA comprising in a molecule, a reporter gene (a) connected downstream from a transcription control region which substantially consists of a recognition sequence of the ligand-responsive transcription control factor and a minimum promoter, and a selective marker gene (b) and that based upon this deficiency alone, the Office has failed to present a valid *prima facie* case of obviousness.

Applicant's arguments have been carefully considered and have been respectfully found unpersuasive for the following reasons. Applicant's assertion that the lower background activity with regard to transcription regulated by the transcription control region of the instant invention and Applicant's further assertion that the lower background activity allows for higher sensitivity in the detection of ligand-responsive transcription activity is not relevant because no recitation of such assertions are present in the instant claims. The combined references do indeed disclose a DNA comprising in a molecule a reporter gene (a) connected downstream from a transcription control region which substantially consists of a recognition sequence of the ligand-responsive transcription control factor and a minimum promoter, and a selective marker gene (b) as presented in the above rejections. In fact, more

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than one example of prior art teaching such a cell comprising the recited DNA has been provided.

Claims 20, 22 and 25-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mader et al (US Patent No. 5,512,483; of record) in view of Carter et al (*P.N.A.S.* **81**:7392-7396, 1984). **This is a new rejection.**

NOTE: For this rejection only, Examiner has interpreted the claims to encompass animal cells stably transformed with a DNA comprising in a molecule, a reporter gene (a) connected downstream from a transcription control region, in which said transcription control region contains a ligand-responsive transcription control factor recognition sequence and a minimum promoter as the main functional element relating to transcription control and a selectable marker (b), but does not contain a reporter gene (c) which is not responsive to said transcription response element, said reporter gene encoding an exogenous reporter protein such as CAT or luciferase or the equivalent.

Mader et al teach a mammalian expression vector composed of several high affinity glucocorticoid response elements (GREs) placed upstream of a minimal promoter TATA region and which further comprises a reporter gene (CAT) and a selective marker

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gene (see entire document, especially the paragraph bridging columns 2 and 3; and Figure 1). Mader et al further teach that the vector expresses an endogenous gene coding a ligand-responsive transcription control factor (the glucocorticoid receptor), and the cells further do not comprise a reporter such as luciferase or CAT connected downstream from a promoter which transcription activity is not changed by having said LRTF. Mader et al also teach that any number of different kinds of minimal promoters from both mammalian or viral origin could be used in their fusion promoter system (see column 3, lines 35-38).

Mader et al do not teach such a vector/cell wherein the minimal promoter is a mouse metallothionein promoter.

Carter et al teach the use of a minimum promoter which is a mouse metallothionein promoter to drive transcription of a metallothionein-galactokinase fusion gene (see entire document, especially page 7393, paragraph bridging first and second columns; 2<sup>nd</sup> column, last paragraph; and Figure 2). Carter et al further teach that through experiments conducted with a number of 3' deletion mutants, the necessary regulatory information for the metallothionein gene was all located upstream of the transcription start site (see page 7393, 2<sup>nd</sup> column, last paragraph and the results presented in Figure 1A). Carter et al

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further teach that a 5' deletion mutant up to base -34 had basal expression levels but was not induced by cadmium (see page 7394, paragraph bridging first and second columns and Figure 4).

One of ordinary skill in the art would have been motivated to combine the teachings of Mader et al and with the mouse metallothionein minimal promoter taught by Carter et al simply as a matter of designer's choice and because Carter et al teach its utility within a fusion gene.

One of ordinary skill in the art would have had a reasonable expectation of success when combining the references of Mader et al and Carter et al because it was clear from the Mader reference that any number of known minimal promoters could be used in combination with the operative regulatory elements in order to control transcription such that it could be specifically measured and Carter et al teach the use of a functional mouse metallothionein minimal promoter.

### **Conclusion**

No claim is allowed.

Certain papers related to this application may be submitted to the Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94

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(December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is (571) 273-8300. Note: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Any inquiry concerning rejections or objections in this communication or earlier communications from the examiner should be directed to Walter Schlapkohl whose telephone number is (571) 272-4439. The examiner can normally be reached on Monday through Thursday from 8:30 AM to 6:00 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached at (571) 272-0781.

Walter A. Schlapkohl, Ph.D.  
Patent Examiner  
Art Unit 1636

December 20, 2006

  
NANCY VOGEL  
PRIMARY EXAMINER